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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,554	05/26/2006	Hajime Ikeda	00005.001316	5977

5514 7590 02/06/2008

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EXAMINER	
MACAULEY, SHERIDAN R	
ART UNIT	**PAPER NUMBER**
1651	

MAIL DATE	DELIVERY MODE
02/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,554	IKEDA ET AL.	
	Examiner	Art Unit	
	Sheridan R. MacAuley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/20/2006 and 5/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending.

Election/Restrictions

1. Applicant's election of Group I (claims 1-11), *Microbacterium* as the species of microorganism, and a combination of glutamine and alanine as the amino acid(s) in the reply filed on November 13, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claim 12 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-11, insofar as they read upon the elected species, are examined on the merits in this office action.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3, 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kanzaki et al. (Journal of Bioscience and Bioengineering, 2000, 89:602-605; cited in IDS). Claim 1 recites a process for producing a dipeptide which comprises: allowing an

enzyme source and a diketopiperazine wherein one or two kinds of alpha-amino acids or derivatives thereof are condensed with each other to be present in an aqueous medium, said enzyme source being a culture of a microorganism having the ability to produce a dipeptide from a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other or a treated matter of the culture; allowing the dipeptide to form and accumulate in the aqueous medium; and recovering the dipeptide from the aqueous medium (provided that the case in which the diketopiperazine is a diketopiperazine wherein aspartic acid and phenylalanine are condensed with each other and the dipeptide is aspartylphenylalanine is excluded). Claim 3 recites the process according to claim 1, wherein the microorganism having the ability to produce a dipeptide from a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other is a microorganism obtained by a method comprising: (1) the step of culturing test microorganisms using a medium comprising a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other as the sole carbon source or nitrogen source; (2) the step of selecting microorganisms which are recognized to grow in the above step (1); and (3) the step of selecting a microorganism which forms and accumulates a dipeptide in an aqueous medium when the diketopiperazine used in the above step (1) and the microorganisms selected in the above step (2) are allowed to be present in the aqueous medium. Claim 9 recites the method of claim 1 wherein the alpha amino acid is one selected from the group of alanine and glutamine. Claim 11 recites the process according to claim 1 wherein the treated matter of the culture is concentrated culture, dried culture, cells obtained by

centrifuging the culture, or a product obtained by subjecting the cells to drying, freeze-drying, treatment with a surfactant, treatment with a solvent, enzymatic treatment, immobilization, mechanical friction or ultrasonication.

6. Kanzaki teaches a process for producing a dipeptide wherein an enzyme source (a microorganism with the ability to produce a dipeptide from a diketopiperazine) and a diketopiperazine (such as one comprising glycine and leucine or alanine and glycine) are combined in an aqueous medium, allowed to form and accumulate in the medium and recovered from the medium (abstract, p. 602, col. 1, par. 1, p. 603, par. 3-5). Kanzaki teaches that the microbe was obtained by culturing the test microorganisms with the diketopiperazine as a carbon and/or nitrogen source, selecting those which were recognized to grow under those conditions and which form and accumulating a dipeptide in the medium when the diketopiperazine from the above step is included in the medium (p. 602, col. 2, par. 4-5). Kanzaki teaches the use of a concentrated cell culture in the method (p. 603, par. 3-5).

7. Therefore, Kanzaki anticipates all of the limitations of the cited claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-5, 7 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanzaki et al. (Journal of Bioscience and Bioengineering, 2000, 89:602-605; cited in IDS) in view of Yokozeki et al. (WO/2003/010189, see US 2004/0137558 A1 for English translation). Claim 1 recites a process for producing a dipeptide which comprises: allowing an enzyme source and a diketopiperazine wherein one or two kinds of alpha-amino acids or derivatives thereof are condensed with each other to be present in an aqueous medium, said enzyme source being a culture of a microorganism having the ability to produce a dipeptide from a diketopiperazine wherein

two kinds of alpha-amino acids are condensed with each other or a treated matter of the culture; allowing the dipeptide to form and accumulate in the aqueous medium; and recovering the dipeptide from the aqueous medium (provided that the case in which the diketopiperazine is a diketopiperazine wherein aspartic acid and phenylalanine are condensed with each other and the dipeptide is aspartylphenylalanine is excluded). Claim 2 recites the process according to claim 1, wherein the microorganism having the ability to produce the dipeptide produces dipeptides in which the proportion of one kind of dipeptide is 70% or more. Claims 3 and 4 recite the process according to claim 1, wherein the microorganism having the ability to produce a dipeptide from a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other is a microorganism obtained by a method comprising: (1) the step of culturing test microorganisms using a medium comprising a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other as the sole carbon source or nitrogen source; (2) the step of selecting microorganisms which are recognized to grow in the above step (1); and (3) the step of selecting a microorganism which forms and accumulates a dipeptide in an aqueous medium when the diketopiperazine used in the above step (1) and the microorganisms selected in the above step (2) are allowed to be present in the aqueous medium, specifically wherein the microorganism having the ability to produce the dipeptide produces dipeptides in which the proportion of one kind of dipeptide is 70% or more. Claims 5 and 7 recite the process according to claim 1, or a similar process, wherein the microorganism having the ability to produce a dipeptide from a diketopiperazine is a microorganism belonging to the genus *Microbacterium*.

Claims 9 and 10 recite the method of claim 1 wherein the alpha amino acid is one selected from the group of alanine and glutamine, specifically wherein the alpha amino acids are alanine and glutamine and the dipeptide is alanylglutamine. Claim 11 recites the process according to claim 1 wherein the treated matter of the culture is concentrated culture, dried culture, cells obtained by centrifuging the culture, or a product obtained by subjecting the cells to drying, freeze-drying, treatment with a surfactant, treatment with a solvent, enzymatic treatment, immobilization, mechanical friction or ultrasonication.

12. Kanzaki teaches a process for producing a dipeptide wherein an enzyme source (a microorganism with the ability to produce a dipeptide from a diketopiperazine) and a diketopiperazine (such as one comprising glycine and leucine or alanine and glycine) are combined in an aqueous medium, allowed to form and accumulate in the medium and recovered from the medium (abstract, p. 602, col. 1, par. 1, p. 603, par. 3-5). Kanzaki teaches that the microbe was obtained by culturing the test microorganisms with the diketopiperazine as a carbon and/or nitrogen source, selecting those which were recognized to grow under those conditions and which form and accumulating a dipeptide in the medium when the diketopiperazine from the above step is included in the medium (p. 602, col. 2, par. 4-5). Kanzaki teaches the use of a concentrated cell culture in the method (p. 603, par. 3-5). Kanzaki does not teach the use of a microorganism of the genus *Microbacterium* or the use of a diketopiperazine comprising alanine and glutamine to produce the dipeptide alanylglutamine. Kanzaki does not

teach the use of a microorganism having the ability to produce dipeptides in which the proportion of one kind of dipeptide is 70% or more.

13. Yokozeki teaches a process for the production of dipeptides from a microbial cell culture or treated cell culture (see abstract of English translation). Yokozeki teaches that microorganisms of the genus *Microbacterium* are suitable in the process and that members of the genus may be used to produce the dipeptide alanylglutamine (see p. 2, par. 20, p. 8, par. 144, table 1(a) of English translation).

14. At the time of the invention, a process for producing a dipeptide comprising nearly all of the elements of the claimed invention was known, as taught by Kanzaki. It was further known that members of the *Microbacterium* genus were capable of producing the dipeptide alanylglutamine, as taught by Yokozeki. One of ordinary skill in the art would have been motivated to use the method of Kanzaki to produce alanylglutamine because Yokozeki teaches that the compound is a desirable component for serum-free media and that efficient production of the compound is needed in the art (p. 1, par. 2, 6). One would also have been motivated to use *Microbacterium* in the process because this organism was known at the time of the invention to have been capable of producing dipeptides. Furthermore, the selection of a bacterium for production of a known dipeptide would have been a routine matter of experimentation, as taught by Kanzaki, who teaches the claimed screening techniques for the identification of a microorganism with the desired characteristic. It would further have been a matter of routine optimization to screen microorganisms for one in which the production of the desired amino acid is high, such as in the claimed range, because

the efficient production dipeptide was known to have been desirable in the art at the time of the invention. One of ordinary skill in the art would have had a reasonable expectation of success in combining the references to practice the claimed invention because members of the *Microbacterium* genus were known to have been capable of production of the desired dipeptide and the screening methods for testing for the desired activity were known in the art at the time of the invention. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

15. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanzaki et al. (Journal of Bioscience and Bioengineering, 2000, 89:602-605; cited in IDS) in view of Yokozeki et al. (WO/2003/010189, see US 2004/0137558 A1 for English translation) as applied to claims 1-5, 7 and 9-11 above, and further in view of Takeuchu et al. (International Journal of Systematic Bacteriology, 1998, 48:739-747). Claim 1 recites a process for producing a dipeptide which comprises: allowing an enzyme source and a diketopiperazine wherein one or two kinds of alpha-amino acids or derivatives thereof are condensed with each other to be present in an aqueous medium, said enzyme source being a culture of a microorganism having the ability to produce a dipeptide from a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other or a treated matter of the culture; allowing the dipeptide to form and accumulate in the aqueous medium; and recovering the dipeptide from the aqueous medium (provided that the case in which the diketopiperazine is a

diketopiperazine wherein aspartic acid and phenylalanine are condensed with each other and the dipeptide is aspartylphenylalanine is excluded). Claim 2 recites the process according to claim 1, wherein the microorganism having the ability to produce the dipeptide produces dipeptides in which the proportion of one kind of dipeptide is 70% or more. Claims 3 and 4 recite the process according to claim 1, wherein the microorganism having the ability to produce a dipeptide from a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other is a microorganism obtained by a method comprising: (1) the step of culturing test microorganisms using a medium comprising a diketopiperazine wherein two kinds of alpha-amino acids are condensed with each other as the sole carbon source or nitrogen source; (2) the step of selecting microorganisms which are recognized to grow in the above step (1); and (3) the step of selecting a microorganism which forms and accumulates a dipeptide in an aqueous medium when the diketopiperazine used in the above step (1) and the microorganisms selected in the above step (2) are allowed to be present in the aqueous medium, specifically wherein the microorganism having the ability to produce the dipeptide produces dipeptides in which the proportion of one kind of dipeptide is 70% or more. Claims 5-8 recite the process according to claim 1, or a similar process, wherein the microorganism having the ability to produce a dipeptide from a diketopiperazine is a microorganism belonging to the genus *Microbacterium*, specifically *Microbacterium luteolum*. Claims 9 and 10 recite the method of claim 1 wherein the alpha amino acid is one selected from the group of alanine and glutamine, specifically wherein the alpha amino acids are alanine and glutamine and the dipeptide is alanylglutamine. Claim 11

recites the process according to claim 1 wherein the treated matter of the culture is concentrated culture, dried culture, cells obtained by centrifuging the culture, or a product obtained by subjecting the cells to drying, freeze-drying, treatment with a surfactant, treatment with a solvent, enzymatic treatment, immobilization, mechanical friction or ultrasonication.

16. Kanzaki teaches a process for producing a dipeptide wherein an enzyme source (a microorganism with the ability to produce a dipeptide from a diketopiperazine) and a diketopiperazine (such as one comprising glycine and leucine or alanine and glycine) are combined in an aqueous medium, allowed to form and accumulate in the medium and recovered from the medium (abstract, p. 602, col. 1, par. 1, p. 603, par. 3-5). Kanzaki teaches that the microbe was obtained by culturing the test microorganisms with the diketopiperazine as a carbon and/or nitrogen source, selecting those which were recognized to grow under those conditions and which form and accumulating a dipeptide in the medium when the diketopiperazine from the above step is included in the medium (p. 602, col. 2, par. 4-5). Kanzaki teaches the use of a concentrated cell culture in the method (p. 603, par. 3-5). Kanzaki does not teach the use of a microorganism of the genus *Microbacterium* or the use of a diketopiperazine comprising alanine and glutamine to produce the dipeptide alanylglutamine. Kanzaki does not teach the use of a microorganism having the ability to produce dipeptides in which the proportion of one kind of dipeptide is 70% or more.

17. Yokozeki teaches a process for the production of dipeptides from a microbial cell culture or treated cell culture (see abstract of English translation). Yokozeki teaches

that microorganisms of the genus *Microbacterium* are suitable in the process and that members of the genus may be used to produce the dipeptide alanylglutamine (see p. 2, par. 20, p. 8, par. 144, table 1(a) of English translation).

18. As discussed above, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kanzaki and Yokozeki to arrive at a method of producing dipeptides comprising nearly all of the claimed elements. Neither reference, however, teaches the use of *Microbacterium luteolum* in the claimed method.

19. Takeuchi teaches a proposed pylogeny for the genus *Microbacterium*, of which *Microbacterium luteolum* is known to be a member (abstract)

20. At the time of the invention, a process for producing a dipeptide comprising nearly all of the claimed elements was known, as taught by Kanzaki and Yokozeki. *Microbacterium luteolum* was also a known member of the *Microbacterium* at the time of the invention. One of ordinary skill in the art would have been motivated to use *Microbacterium luteolum* in the combined process of Yokozeki and Kanzaki because Kanzaki teaches that microorganisms of the *Microbacterium* genus were suitable for the production of dipeptides. The selection of a bacterium for production of a known dipeptide would have been a routine matter of experimentation, as taught by Kanzaki, who teaches the claimed screening techniques for the identification of a microorganism with the desired characteristic. One of ordinary skill in the art would have had a reasonable expectation of success in combining the references to practice the claimed invention because members of the *Microbacterium* genus were known to have been

capable of production of the desired dipeptide and the screening methods for testing for the desired activity were known in the art at the time of the invention. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

21. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan R. MacAuley whose telephone number is (571) 270-3056. The examiner can normally be reached on Mon-Thurs, 7:30AM-5:00PM EST, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SRM
/Ruth A Davis/

Primary Examiner, AU 1651